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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,382	REUBINOFF ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-46, 51, 56-58, 60-68, 86-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46,51,56-58,60-68 and 86-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Response and Amendment, filed 11/22/04, has been entered. Claims 39, 41-45, 51, 56, 60, 62, 64, 88, 89 have been amended. Claim 95 has been added. Claims 39-46, 51, 56-58, 60-68, 86-95 are pending and under current examination.

Information Disclosure Statement

Applicants' Information Disclosure Statements, filed 6/30/04, 1/18/05, 5/30/04 have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-46, 51, 56-58, 60-68, 86-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The claims are directed to methods of inducing somatic differentiation of stem cells *in vitro* into neural progenitor cells, where said neural progenitor cells are identified by the expression of at least one of NCAM, nestin, vimentin, or Pax-6 and by the lack of expression of Oct-4, said method comprising: obtaining undifferentiated human pluripotent embryonic stem cells; and providing a controlled differentiating condition which is non-permissive for stem cell renewal, does not kill cells or induce unidirectional differentiation toward extraembryonic lineages (claims 39-46). In other embodiments, the claims are directed to methods of differentiating neural progenitor cells to somatic cells (claims 51, 56-58, 60-63, 86, 87); methods of producing enriched preparations of human ES cell derived neural progenitor cells (claims 64-68, 89-94), methods of inducing somatic differentiation of stem cells into neural progenitor cells (claims 88 and 95).

The specification teaches culturing human ES cells in serum-free conditions in order to produce neural progenitor cells. The specification teaches the

characterization of the neural progenitor cells by specific markers (NCAM, nestin, vimentin. The specification teaches the directing of differentiation to glial cells by plating the neural progenitor cells in a medium supplemented with PDGF-AA and T3 (which induces maturation of oligodendrocyte precursors). See p. 82, part (e). Although the method steps as claimed are found to be adequately described, what is found to lack an adequate written description is the generation and identification of the neural progenitor cells. For example, certain embodiments are directed to identifying neural progenitor cells by specific markers, for example, NCAM, nestin, vimentin or Pax-6. Certain claims fail to provide any identification step for the neural progenitor cells. Thus, the specification fails to provide adequate written description of the neural progenitor cells that are produced by the claimed method, because identification of the neural progenitor cells by one particular marker (or unspecified combinations thereof) or by no marker at all, fails adequately describe the neural progenitor cells. This is because the markers recited are found in other cell types. For example, NCAM is found during early embryonic development, in the derivatives of all three germ layers, and after birth is restricted to neural tissues. See Cremer *et al.* [**Mol. and Cell. Neuro.**, 8:323-335 (1997)], especially p. 323, 2nd column, 1st full ¶. Further, Pax-6 is found to be important in the development of the eye [see Bäumer *et al.*, **Development**, 129:4535-4545 (2002)]. It is found that nestin is expressed in islet cells [see Wang *et al.*, **J. Endocrin.**, 184:329-339 (2005)]. Thus, the identification of neural progenitor cells by a particular marker (or a unspecified

combination of the recited markers) fails to adequately describe a neural progenitor cell, and thus, there is no particular description of the neural progenitor cells to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described the specification and which are not conventional at the time of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the invention as a whole) such that a person of skill in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the embodiments of neural progenitor cells lacks a written description, because the specification fails to provide relevant identifying characteristics, and the neural progenitor cells are found to be essential to the claimed invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is a part of the invention a reference to a method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to

be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claims 39-46, 51, 56-58, 60-68, 86-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The invention is directed to the somatic differentiation of human embryonic stem cells *in vitro* to produce neural progenitor cells.

Breadth of the claims. The claims are directed to methods of inducing somatic differentiation of stem cells *in vitro* into neural progenitor cells, where said neural progenitor cells are identified by the expression of at least one of NCAM, nestin, vimentin, or Pax-6 and by the lack of expression of Oct-4, said method comprising: obtaining undifferentiated human pluripotent embryonic stem cells; and providing a controlled differentiating condition which is non-permissive for stem cell renewal, does not kill cells or induce unidirectional differentiation toward extraembryonic lineages (claims 39-46). In other embodiments, the claims are directed to methods of differentiating neural progenitor cells to somatic cells (claims 51, 56-58, 60-63, 86, 87), methods of producing enriched preparations of human ES cell derived neural progenitor cells (claims 64-68, 89-94), methods of inducing somatic differentiation of stem cells into neural progenitor cells (claims 88 and 95).

Guidance of the Specification/The Existence of Working Examples. The specification is directed to the production of differentiated cells, and in particular, neural progenitor cells, from human embryonic stem (hES) cells. The specification teaches that the hES cells express markers for the human pluripotent stem cells, including SSEA-4, GCTM-2 antigen, TRA 1-60, and express Oct-4. See p. 7, lines 8-13. The specification teaches that hES cells characterized (see p. 62-63 and Examples 1-2) and then induced to differentiate into neural precursors by culturing the cells in serum free medium that was supplemented with EGF, bGFG, DMEM/F12, B27 supplementation, glutamine, then mechanically dissecting the

cells and supplementing some of the cells in a serum-free medium with heparin. See pp. 64-65. The cell clusters formed round spheres, which were then characterized to see what proportion of the cells expressed NCAM, nestin and vimentin. See p. 66, #7. RT-PCR was then used to study the expression of nestin, PAX6, oct-4, CD-34, FLK-1, HNF-3, and alpha-fetoprotein in the spheres. See p. 67.

The specification teaches that specific characterization of the ES cell-derived neural progenitor cells, stating that, when allowed to differentiate, the expression of nestin and PAX-6 was seen (Figure 19, Example 5, lines 10-15). In particular, the specification teaches that the proportion of cells in the ES-cell derived spheres expressing NCAM, nestin and vimentin were calculated. It was found that 99 and 95.5% of the cells stained positive for NCAM, and that 96.6% and 73.1% of the cells stained positive for nestin and vimentin, respectively. Further, that these markers were expressed by 66.8% and 58% of the cells originating from the spheres. See pp. 79-80, bridging ¶. The specification teaches the directing of differentiation to glial cells by plating the neural progenitor cells in a medium supplemented with PDGF-AA and T3 (which induces maturation of oligodendrocyte precursors). See p. 82, part (e).

State of the Art/Predictability of the Art. The state of the art of directed differentiation is found to be unpredictable with regard to generation of a particular cell type. Thus, specific guidance must be provided in order to enable the claimed

invention. Verfaillie *et al.* [**Hematology** (Am Soc Hematol Educ Program). 2002;:369-91] who review the state of the art of stem cells, teach, that, with regard to the directed differentiation of ES cells, "Many proposed applications of human ES cells are predicated on the assumption that it will be possible to obtain pure populations of differentiated cells from the ES cultures. It might be envisioned that in order to achieve this one would treat ES cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice, that has not proven possible with the mouse system." See p. 278, 2nd column, Differentiation in vitro. They further teach that a range of approaches have been attempted to produce a highly homogenous population of differentiated cells from ES cells, for example, relying upon the spontaneous differentiation of the ES cells to embryoid bodies. However, embryoid bodies contain a range of differentiated cells, which is a recognized limitation of directed differentiation of ES cells. Verfaillie teach that the ES cells can be treated with particular agents/factors that can drive differentiation along a specific lineage (see p. 379, 1st column, 1st full ¶). However, it is clear that directed differentiation of ES cells to generate a particular cell type of interest is unpredictable. Thus, specific guidance must be provided to enable the claimed invention.

The Amount of Experimentation Necessary. The claims, as broadly written, are not enabled. Although the specification provides conditions for inducing somatic differentiation (*i.e.*, serum free conditions with specific growth factors) of hES cells

and the characterization of cells differentiated from the hES cells that have particular markers, the invention is not enabling, because the claims recite that the neural progenitor cells are identified by expression of at least one of the markers (NCAM, nestin, vimentin or Pax-6). This is not found to be enabling because the expression of at least one of the markers would not allow the skilled artisan to arrive at the claimed invention, producing neural progenitor cells. This is because the expression of any one of the markers fails to provide any specific information for the generation of neural progenitor cells. For example, NCAM is found during early embryonic development, in the derivatives of all three germ layers, and after birth is restricted to neural tissues. See Cremer *et al.* [**Mol. and Cell. Neuro.**, 8:323-335 (1997)], especially p. 323, 2nd column, 1st full ¶. Further, Pax-6 is found to be important in the development of the eye [see Bäumer *et al.*, **Development**, 129:4535-4545 (2002)]. It is found that nestin is expressed in islet cells [see Wang *et al.*, **J. Endocrin.**, 184:329-339 (2005)]. Thus, the claims, which recite that the cells express one of these above-recited markers, fails to provide an enabling disclosure to produce neural progenitor cells. There is no specific guidance provided by the specification with regard to characterization of cells that express one or more of the markers, NCAM, nestin, vimentin or Pax-6, for example, the specification fails to provide guidance or teachings with regard to cells that express combinations of the recited markers.

Accordingly, in view of the unpredictable state of the art of directed differentiation, the lack of teaching or guidance provided by the specification with regard to the generation of neural progenitor cells which express at least one of NCAM, nestin, vimentin or Pax-6 (or a combination thereof), the art which teaches that the above-recited markers are found in cell types other than neural progenitor cells, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 102

The prior rejection of claims 39-46 under 35 U.S.C. §102(b) as being anticipated by Shamblott *et al.* is withdrawn because of Applicants' recitation of specific expression markers (NCAM, nestin, vimentin or Pax-6) to identify the neural progenitor cells. Shamblott teaches that immunohistochemical analysis of the embryoid bodies revealed expression of neurofilament (see Table 1, and p. 13729, col. 2, 1st full ¶) but do not specifically recite the particular markers recited in the as-amended claims. It is noted that Applicants argue that Shamblott do not teach a "controlled differentiating condition to obtain a homogenous population of neural progenitor cells." See p. 10-11 of the Response. This argument is not found to be persuasive because no such limitation exists in the claims. Particularly, there is no definition provided by the specification with regard to a "controlled differentiating condition" and further, that there is no limitation in the claims with

regard to the generation of a homogenous population of neural progenitor cells. See also, prior Office action, pp. 4-5.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The prior rejection of claim 51, and newly added claim 95, under 35 U.S.C. 103(a) as being obvious over Thomson in view of Brustle, is maintained for reasons of record.

Applicants argue that the references fail to teach or suggest the claimed method. Firstly, that neither Thomson nor Brustle teach or suggest inducing differentiation the progenitor cells by growing them in *serum free media* in the presence of growth factors and then withdrawing the growth factors. Applicants point to Thomson to show that the hES cells were cultured in media containing 20% FBS, and Brustle, to show that the EBs were formed in media containing 20% FBS. See p. 13, 1st full ¶ of the Response. This is not persuasive. The claim requires that the neural progenitor cells are grown on an adhesive substrate in the presence of serum free media and growth factors, and then inducing the cells to differentiate by withdrawal of the growth factors. See lines 6-8 of claim 51. Thus, it is clear from the method steps that the progenitor cells are formed prior to the culturing in serum free media. Furthermore, upon closer inspection, it is noted that Brustle teaches that the ES cell lines were grown in the 20% FBS, but when they were induced to form embryoid bodies, they were cultured onto gelatin coated dishes, and then, further, that the 4-day old embryoid bodies were cultured in ITSFn medium, which does not contain FBS. See p. 756, #7.

Applicants argue that although Thomson suggests that hES cells can be differentiated into somatic cells, they do not provide any substantive teachings for an *in vitro* differentiation conditions. Further, that there is no indication that any neural progenitor cells were actually derived *in vitro* from undifferentiated hES cells. Applicants argue that the precursor cells, as disclosed by Brustle et al. were

derived from mouse ES cells, and that although Thomson suggest that progresses made in the differentiation of mouse ES cells into somatic cells would be useful to direct the differentiation of hES cells, neither Thomson, nor Brustle teach or suggest *how* the information obtained from differentiating mouse ES cells can be used to successfully differentiate human ES cells. Applicants point to Shamblott, who identified neural cells in EBs which were generated from mouse ES cells only with the addition of hrLIF to the cell culture. Applicants point that LIF is not required for the induction of somatic differentiation of human ES cells, and that because human and mouse ES cells have different conditions for growth and differentiation, those skilled in the art would not have reasonably expected that the conditions for differentiation of mouse ES cells, as disclosed by Brustle, would be applicable to differentiation of human ES cells. See pp. 13-14 of the Response.

This is not persuasive. Firstly, it is noted that Shamblott teaches that human PGCs, in the presence of hrLIF form embryoid bodies, not from mouse ES cells, as argued by Applicants. See p. 13729, bridging ¶, col. 1-2. It was analysis of these EBs that indicated antineurofilament-reactive cells. See p. 13729, 2nd column, 1st full ¶ and Table 1. It is well known in the ES cell art that human ES cells remain undifferentiated when grown on mouse ES fibroblast feeder layers, but differentiate or die in the absence of fibroblasts, even in the presence of LIF. Thus, the art recognizes that although mouse ES cells remain undifferentiated in the presence of LIF, and differentiate in the absence of LIF, the presence of LIF alone is

not sufficient to maintain hES cells in the undifferentiated state. See Thomson *et al.*, **PNAS**, 92 :7844-7848 (1998), cited in the Information Disclosure Statement, filed 7/2/01, #5. Thus, the differences between mouse and human ES cells are found to be in the maintaining of the ES cells, but not the differentiation of the cells. For example, Mizuseki *et al.* [PNAS, 100(10):5828-5833 (2003)] provide such evidence by culturing mouse and primate ES cells under the same conditions to produce neural cells. See p. 5832, 1st column. Although they teach different yields of neural cells between primate and mouse ES cells, they teach that both cells produce neural cells under the same conditions. Accordingly, in it maintained that at the time of the instant invention, it would have been obvious for one of skill in the art to culture human ES cells, as taught by Thomson, in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form glial precursors, and then in the absence of the growth factors to induce the formation of astrocytes and oligodendrocytes, as taught by Brustle to provide differentiated cells for drug discover and/or transplantation therapies, with a reasonable expectation of success. The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The prior rejection of claims 56-58 and 86 under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. in view of Brustle et al. and Stemple et al. is maintained for reasons of record.

Applicants present the same arguments, as above, with regard to Thomson and Brustle, namely, that neither Thomson nor Brustle suggest or teach inducing differentiation of progenitors by growing the cells in serum free media. See p. 16, 3rd ¶ of the Response. This is not persuasive. As stated previously, Brustle teaches that the ES cell lines were grown in the 20% FBS, but when they were induced to form embryoid bodies, they were cultured onto gelatin coated dishes, and then, further, that the 4-day old embryoid bodies were cultured in ITSFn medium, which does not contain FBS. See p. 756, #7. Thus, Brustle teach growing the progenitor cells in a serum free medium. Applicants further argue (as previously) that neither Thomson nor Brustle suggest neural progenitor derived cells from undifferentiated human ES cells, much less a method of inducing differentiation of such progenitor cells. See p. 16, 1st ¶. This is not persuasive. As stated previously, the art recognizes that although the maintenance of undifferentiated mouse and human ES cells requires different conditions, namely the presence or absence of LIF, the motivation to utilize mouse ES cells differentiation protocol to differentiate human ES cells is found in the art, and further, that the differentiation protocol often result in the same cell types.

With regard to Stemple, Applicants argue that the differentiation conditions recited are directed to neural crest cells, which are not neural progenitor cells derived *in vitro* from pluripotent ES cells, and that those of skill in the art would not have had any reasonable expectation that the culturing conditions as taught by Stemple would be applicable to neural progenitor cells derived from ES cells. See p. 16, 4th ¶ of the Response. This is not found to be persuasive. First, the claims require that the neural progenitor cells are derived from human ES cells. Thus, a neural crest cell is originally derived from an ES cell. Further, it is maintained that Stemple's teachings provide sufficient motivation to reach the claimed invention because they teach the requirement of poly-D lysine, and the growth of neural stem cells in the presence retinoic acid. Thus, it is maintained that, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells, as taught by Thomson, in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form neural precursors, as taught by Brustle, but growing in the precursors in a media comprising retinoic acid and growth on poly-D-lysine and laminin coated plates to induce neuronal growth, as taught by Stemple, for drug discover and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to arrive at the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The prior rejection of claims 60-63 and 87 under 35 U.S.C. 103(a) as being unpatentable over Thomson, Brustle, Stemple and Ben-Hur is maintained for reasons of record.

Applicants' arguments regarding Thomson, Brustle and Stemple, have been addressed above. Applicants argue that Ben-Hur does not cure the deficiencies in the art of Thomson, Brustle and Stemple because they do not teach or suggest neural progenitor cells from undifferentiated human pluripotent ES cells. Applicants argue that because Ben-Hur teach neural tissue isolated from newborn rats, and not human neural progenitors derived from human ES cells, there is no reasonable expectation that the conditions for differentiation the cells, as taught by Ben-Hur, would be applicable to the instant invention. See p. 19, 1st ¶ of the Response.

This is not persuasive. The claims require that the neural progenitor cells be "derived from" ES cells. Thus, although Ben-Hur do not teach cells derived from ES cells, they do teach cells that are neural progenitor cells. Thus, the conditions that Ben-Hur teach would be applicable to the claimed invention, because, as stated previously, it would be obvious for one of skill in the art to use techniques used in the differentiation of mouse ES cell art and apply these techniques to human ES cells. As stated previously, the differences between human and mouse ES cells, as recognized by the art, are in the culturing conditions to maintain the cells in an

undifferentiated state. Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, at the time of filing, to culture the human ES cells, as taught by Thomson in DMEM/F12 media in the presence of FGF and PDGF-AA, on polyornithine to form glial precursors and then, in the absence of growth factors, to form predominantly oligodendrocytes and astrocytes, as taught by Brustle, but growing the precursors on poly-D-lysine and fibronectin coated plates, in order to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation, followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes, and glia cells for drug discover and/or transplantation therapies.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The prior rejection of claims 64-68 and 88-94 and claims 39-46, as amended, rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson, Brustle and Ben-Hur is maintained for reasons of record.

Applicants present the same arguments with regard to Thomson, Brustle and Ben-Hur, and submit that there is no showing or suggestion in the cited references to develop a homogenous population of neural progenitor cells, that are an intermediate cell type, and that are not pluripotent cells but are multipotent neural

progenitor cells that will always provide a neural type of cell, either neurons, astrocytes or oligodendrocytes. See p. 20, 1st ¶ of the Response.

This is not persuasive. Applicants are reciting limitations that are not in the claims. There is no requirement for the preparation of neural progenitor cells be a homogenous population of cells. Further, Applicants' arguments, with regard to the application of methods taught in the mouse ES cell art, and the neural progenitor cell art, to differentiation of human ES cells, has been addressed above. See p. 20, 2nd ¶.

Accordingly, it is maintained that, at the time of the claimed invention, it would have been obvious for one of ordinary skill in the art, to produce oligodendrocytes by culturing the human ES cells, as taught by Thomson in DMEM/F12 media, in the presence of FGF2 and EGF to form glial precursors, as taught by Brustle, and to further culture the glia cells in the presence of B27, FGF2 and EGF in combinations to provide oligodendrocytes for drug discover and/or transplantation. The cited art provides sufficient suggestion, teaching and motivation to achieve the claimed invention. The term "include" has been broadly interpreted to mean that the three growth factors, B27, FGF2 and EGF, are used in various combinations.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
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